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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	ART UNIT	PAPER NUMBER
LEE, G	1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/295,663	Joshi et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____3___ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-55* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____7___

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Objections

Claim 35 is objected to because of the following informalities: nucleic acid is misspelled in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of cancer cells, said method comprising administering to a cancer patient an amount of vincristine sulfate and cisplatin that is effective to synchronize cancer cells inhibitory, at or around the site of the tumor, administering to said cancer patient a tumor gene well known in the art that wherein the expression of said tumor inhibitory gene inhibits the growth of said cancer cells, does not reasonably provide enablement for a method of administering any and all cancerous cells with any and all cell cycle synchronizer/blocker in any and all mammalian hosts and achieving "treatment" via administering a cell cycle synchronizer and any and all tumor suppressor gene that transforms cancer cells wherein the tumor suppressor gene product inhibits the growth by inducing apoptosis of said cancer cells and delivered by any and all routes of administration. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of inhibiting the growth of cancer cells comprising administering to an amount of a cell cycle synchronizer that is effective to synchronize cancer cells of a patient at a first stage of the cell cycle; and administering to said cancer patient a nucleic acid that transforms cancer cells of the said patient; wherein the expression of said nucleic acid inhibits the growth of said cancer cells.

The claimed invention is directed to effecting gene therapy by way of administering any and all cancerous cells with any and all cell cycle synchronizer/blocker in any and all mammalian hosts by any and all routes of administration and achieving "treatment" via administering a cell cycle synchronizer and any and all tumor inhibitory gene that transforms cancer cells wherein the tumor suppressor gene inhibits the growth by inducing apoptosis of said cancer cells. While, in the Examples, the specification teaches vincristine sulfate as the synchronizing/blocking agent and IL-12 or HSV-TK in a liposome complex to observe tumor growth inhibition and regression in tumor size (pages 54-57). The specification utilizes 25 C57 mice were seeded intraperitoneally by injection B16 cells follow by vincristine sulfate encapsulated in sphingomyelin-containing TCS injection via tail vein at 7 days post injection of cells and after 24 hours all mice are injected i.p. with TCS containing luciferase plasmid pINEX L018 as support for enablement of the claimed methodology for administration any and all therapeutic nucleic acid efficient transformation. Another example, the specification illustrates synchronization of

cells at a tumor site by injecting mice carrying MCA 207 tumors and injecting them with empty OncoTCS or OncoTCS with vincristine sulfate to demonstrate vincristine sulfate synchronized cell cycle distribution in approximately 85% (G0/G1), 5% (S) and 10% (G2/M) (page 50). Several other examples illustrated reporter gene improved transfection following treatment with cell cycle blocking agent and several combination therapy was demonstrated with vincristine and pINEX-IL-12 or HSV-tk/ganciclovir in mice (pages 56-57).

With regards to extrapolating from the mice models of the specification to treating cancer, the importance of relevant animal models for support of enablement is imperative in the determination of effectiveness of treatment or effect of vectors in gene therapy. With regards to extrapolating from *in vitro* data of the specification to gene therapy of a disease, the importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy. This observation is supported by Orkin et al. in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (see pages 10-11 and 14). On page 11, second and third paragraphs, Orkin et al emphasize the importance of relevant animal models, and state that many "mouse models often do not faithfully mimic the relevant human conditions." Orkin et al also indicated that when dealing with cancer, the relevance of animal models appears to be less predictive than with other single-gene disorders. Note that the expression levels have not been demonstrated with regard to rendering treatment to a model for cancer.

While the claimed invention is directed to any and all tumor inhibitory gene, the claims also encompass any and all route of administration comprising the therapeutic gene i.e. HSV-TK and follow by ganciclovir to treat patients with cancer. Furthermore, the effect of any and all tumor inhibitory gene by any and all route of administration as therapy for cancer is unpredictable in the art. Bischoff et al disclosed the limitations of intratumorally delivery in Science, Vol. 274: 373 (1996). Bischoff et al teach that the ability of the virus to spread to distant sites and to infect metastatic tumor cells needs to be addressed because direct intratumoral injection limits the potential benefit of this approach to accessible tumors (primary brain tumors and cancers of the head and neck, for example). Dachs et al (1997) further state that advances in gene therapy have been made using viral and nonviral methods, but effective and selective delivery of DNA to tumor cells remains a complex task due to a poor and disorganized blood supply, and high interstitial fluid pressure of a solid tumor (p 314, col. 1, parag. 2). As for targeting, Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery (targeting) for the breadth of the claimed invention. Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of

the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate

enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While applicants specification supports efficient transfer for *in vivo* direct injection into the tumor, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. Instead, the specification only teaches a tumor suppressor gene such as HSV-Tk gene and a cell cycle synchronizer/blocker such as vincristine as an indicator that potential use of combining vincristine which synchronizes cells at a first stage of the cell cycle follow by administration of HSV-Tk nucleic acid follow by an activator such as ganciclovir for the destruction of cancer cells.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art and effective treatment for cancer therapy. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease (i.e., HSV-TK) providing a specific therapeutic effect, gene therapy as a

broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy nor shown direct correlative effect of inhibiting the growth of cancer cells, despite the *in vitro* demonstration of effective transduction of the cancerous cells with HSV-TK or marker gene and administration of vincristine of the Examples in the specification. The breadth of the claims is drawn to any and all tumor inhibitory genes which can treat any and all types of cancer in gene therapy, while the specification list numerous genes, the specification fails to teach the demonstration of any other type of tumor inhibiting gene other than HSV-TK which is well known in the art as a gene to treat cancer but it is not representative of treating or inhibiting any and all tumor inhibiting gene in gene therapy. However, it appears from these teachings, that several parameters of the claimed invention are critical to achieving such treatment, particularly, route of delivery, parameters such as specific dosages of cell cycle synchronizer, specific dosages of nucleic acid necessary for a therapeutic effect, targeting of gene transfer to specific cells (selectivity of gene transfer), promoters to regulation gene expression or the combination effect of cell cycle synchronizer and specific gene transfer need to be addressed. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of cancer by an amount any and all tumor inhibitory gene, in

particular when used in combination with gene therapy for treatment if any and all types of cancer, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to achieving treatment of inhibiting the growth of cancer without addressing targeting, construct for delivery, route of administration, gene expression, dosage for therapeutic effect using any and all tumor inhibitory gene of interest and any and all cell cycle synchronizer, in particular in the absence of a clinically relevant animal for gene therapy of any and all types of cancer, and the breadth of the claims directed to the use of enormous number of gene, any gene therapy delivery construct and any cell cycle synchronizer/blocker alone or in combination, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-37 are vague and indefinite for its recitation of " cell synchronizer or synchronizes" because it is unclear as to what is encompassed in the claim as to what mechanism

is provide by synchronizing wherein the cells are all in the same phase at the same time or that the cells stops within phases. The metes and bounds of the claims can not be determined.

Claims 38-55 are vague and indefinite for its recitation of "cell cycle blocker" because it is unclear as to what factors is encompassed in the claim to determined the cell cycle to be blocked or not blocked and are all cells blocked at the same phase. The metes and bounds of the claims can not be determined.

Claims 3 and 16 are vague and indefinite for its recitation of the terms "substantially " because it is unclear what standards are encompassed in the claim to determine the nuclear membrane that would be considered to substantially degraded. What level of degradation is substantial and what level is not substantial of the nuclear membrane? The metes and bounds of claims 3 and 16 cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 8, 10-14, 15-16, 21, 23-32, 35, 38-44, 46-47, 49, 52 and 55 are rejected under 35 U.S.C. 102(e) as being anticipate by Roth et al (U.S.Patent #5,747,469).

Roth et al disclose the use of tumor suppressor (p53) genes in an adenovirus-mediated gene transfer in combination with a DNA damaging agent (i.e. cisplatin) or factor for use in killing cells and in particular cancerous cells in vivo wherein treated cells underwent apoptosis with specific DNA fragmentation by direct injection of the p53-adenovirus construct into tumors subcutaneously (abstract). Note, it is an inherent property of cisplatin, vinca alkaloid and taxol as therapeutic agent which are can induce cell cycle arrest for cancer treatment. Roth et al disclose a gene transfer and chemotherapeutic agent (p53 or HSV-Tk) effect separately as well as in combination (either order of delivery) for destruction of the tumors or cancerous cells. Roth et al also disclose several viral and non-viral methods of delivering (claim 88) the therapeutic gene (claims 14-15 and 19-21), several DNA damaging agent (claims 4, 6, 8 and 10-12) at several dosages (claims 5, 7, 9), vector is administered prior/after/or at the same time of DNA damaging agent (claims 35-37), several types of cancer (claims 41-48) and several promoter (see claims). Roth et al further disclose the elevated intracellular p53 protein levels in cells that are in the process of apoptosis. Inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death and thus, p53 contribute to the induction of apoptotic tumor cell death by chemotherapeutic agents (column 28, example 7). Thus, Roth et al clearly anticipated claims 1-3, 8, 10-14, 15-16, 21, 23-32, 35, 38-44, 46-49, 52 and 55 of the instant invention.

Claims 1-3, 8, 15-16, 21, 28, 32-34, 38, 41, 44, 46, 47, 49-51 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Son et al, Proc. Natl. Acad. Sci USA (1994), Vol. 91: 12669-12672.

Son et al disclose that human ovarian carcinoma cells (line 2008) grown as subcutaneous solid tumor in the severe combined immunodeficient mouse can be transfected by directly injecting a plasmid DNA-liposome complex into the tumor (abstract). Son et al further disclose that the level of reporter gene expression in the tumor cells was significantly elevated if the animal received a single i.p. injection of cisplatin 1 week before the lipofection and thus, sensitizing the tumor cells (abstract). Son et al suggest a sequential combinational gene therapy protocol with cisplatin for the ovarian carcinoma. Son et al teach that cationic liposomes were composed of 3β[*N*-(*N*', *N*'-dimethylaminoethane)carbamoyl]cholesterol (DC-chol) and dioleoyl phosphatigylethanolamine, 3:2 (mol/mol) and mixed with pUCCMVCAT for injection directly into the tumor in three sites (p. 12669, Materials and Methods). Son et al further teach that human ovarian tumors of animals without cisplatin injection were inefficiently transfectable with either DNA alone or with a DNA-liposome complex (p. 12670, column 1) due to variations in the degree of transfection between animals. Son et al also disclose other anticancer drugs that have/ have not similar tumor sensitization effect on tumor cells and thus, the enhanced sensitivity to lipofection seems to be limited to the tumor cells of the cisplatin-treated animals (p. 12671, column 2). Thus, Son et al clearly anticipated claims 38, 47 and 50-51 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-7, 9, 15, 17-20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krek et al, Methods Enzymol. (1995), Vol. 254: 114-24 taken with Roth et al (U.S. Patent #5,747,469) and Lee et al, Cancer Res. (1996), Vol. 56(6): 1303-8.

Krek et al disclose methods for particular cell line arrest at a specific point in the cell cycle in response to the various treatments such as serum starvation and metabolic agents for synchronizing of continuously dividing cells (p. 115). Krek et al further disclose that doubling time is the minimum time of exposure to the drug required to synchronize an asynchronous population of cells and also the minimum concentration of the drug of choice to enrich for cells in a particular phase of the cell cycle must be determined or overexposure will lead to cell death and irreversible cell damage. Krek et al differ from the claims in that it fails to disclose the

combination of a cell cycle synchronizer and gene transfer that encodes a desired gene product. However, the secondary references, Roth et al and Lee et al, cure the deficiency. Roth et al disclose the therapeutic potential of combination apoptotic gene transfer and chemotherapeutic agents against cancer and that to realize the therapeutic potential, alternative cell cycle synchronizer/blockers are needed. Roth et al disclose the use of tumor suppressor (p53) genes in an adenovirus-mediated gene transfer in combination with a DNA damaging agent (i.e. cisplatin) or factor for use in killing cells and in particular cancerous cells in vivo wherein treated cells underwent apoptosis with specific DNA fragmentation by direct injection of the p53-adenovirus construct into tumors subcutaneously (abstract). Roth et al disclose various modes of gene delivery as well as various DNA damaging agent/chemotherapeutic agents for the treatment of cancer. Roth et al disclose the elevated intracellular p53 protein levels in cells that are in the process of apoptosis. Inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death and thus, p53 contribute to the induction of apoptotic tumor cell death by chemotherapeutic agents (column 28, example 7). Lee et al disclose Taxol for the treatment of both primary and drug-resistant ovarian cancer. Lee et al further disclose the Taxol is known to stabilize microtubules and block cell mitosis that is more effective than other antimitotic agents such as vinblastine and colchicine and that it has both antimitotic and apoptosis-inducing activity (abstract and column 1). Note, it is well known in the art that cisplatin and taxol (taxol is another vinca alkaloid) are some of the therapeutic agent which can

induce cell cycle arrest for cancer treatment and that various combination of conventional drugs are known in the art. It would have been obvious to one of ordinary skill in view of the teachings of Lee et al to use Taxol, cisplatin and any of the other vinca alkaloids or platinum coordination complexes in combination with therapeutic gene transfer for the treatment of cancer.

Roth et al provide the motivation to combine the references. Roth et al disclose the therapeutic potential of gene transfer and chemotherapeutic agents against cancer and that to realize the therapeutic potential, alternative cell cycle synchronizer/blockers are needed. Roth et al disclose the use of tumor suppressor (p53) genes in an adenovirus-mediated gene transfer in combination with a DNA damaging agent (i.e. cisplatin) or factor for use in killing cells and in particular cancerous cells in vivo wherein treated cells underwent apoptosis with specific DNA fragmentation by direct injection of the p53-adenovirus construct into tumors subcutaneously (abstract).

Regarding claims 4-6 and 17-19, Krek et al disclose methods for particular cell line arrest at a specific point in the cell cycle in response to the various treatments such as serum starvation and metabolic agents for synchronizing of continuously dividing cells (p. 115). It would have been obvious in view of the teachings of Roth et al and Lee et al to combine therapeutic gene transfer and cell cycle synchronizer (cisplatin, taxol and other vinca alkaloid) together for increase efficiency of transformation and to inhibit the growth of cancer cells.

Accordingly, the ability of drug induced cell synchronization of Krek et al by the method of combination therapy as suggested of Roth et al and Lee et al in order to obtain efficient,

enhance delivery of therapeutic gene to inhibit growth of tumor cells was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 15, 36-38, 45 and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Son et al, Proc. Natl. Acad. Sci USA (1994), Vol. 91: 12669-12672, taken with Roth et al (U.S. Patent #5,747,469).

Son et al disclose a sequential combination therapy with cisplatin followed by gene therapy might be an effective treatment protocol for ovarian cancer and that tumor cells in these patients might be more transfectable with DNA-liposome complex for gene therapy. Son et al further disclose that tumor cell resistant to cisplatin, an anticancer drug, were more transfectable with a cationic liposome-DNA complex than the parent cells (page 12669, column 1). Son et al disclose that human ovarian carcinoma cells (line 2008) grown as subcutaneous solid tumor in the severe combined immunodeficient mouse can be transfected by directly injecting a plasmid DNA-liposome complex into the tumor (abstract). Son et al further disclose that the level of reporter gene expression in the tumor cells was significantly elevated if the animal received a single i.p. injection of cisplatin 1 week before the lipofection and thus, sensitizing the tumor cells (abstract). Son et al suggest a sequential combinational gene therapy protocol with cisplatin for

the ovarian carcinoma. Son et al teach that cationic liposomes were composed of 3β[*N*-(*N'*, *N'*-dimethylaminoethane)carbamoyl]cholesterol (DC-chol) and dioleoyl phosphatigylethanolamine, 3:2 (mol/mol) and mixed with pUCCMVCAT for injection directly into the tumor in three sites (p. 12669, Materials and Methods). Son et al further teach that human ovarian tumors of animals without cisplatin injection were inefficiently transfectable with either DNA alone or with a DNA-liposome complex (p. 12670, column 1) due to variations in the degree of transfection between animals. Son et al also disclose other anticancer drugs that have/ have not similar tumor sensitization effect on tumor cells and thus, the enhanced sensitivity to lipofection seems to be limited to the tumor cells of the cisplatin-treated animals (p. 12671, column 2). Son et al differs from the claims in that the reference fails to disclose the foreign therapeutic gene is fully encapsulated in a lipid formulation such that less than 5% of the gene is degraded after exposure of said formulation to 1U DNAse I for 30 minutes in digestion buffer at 37^{0}C. Note, it is well known in the art of liposome formulation to encapsulated DNA within the liposome complex and that to subject the liposomal complex to DNAse treatment was to remove excess unencapsulated DNA. Thus, it would have been obvious to one of ordinary skill in the art to fully encapsulate the therapeutic gene within a lipid formulation for efficient delivery. Son et al further differs from the claims in that the reference fails to disclose the foreign therapeutic gene is administered at least 32 hours or 48 hours prior to administering cell cycle blocking agent. However, the secondary reference, Roth et al, cure the deficiency. Roth et al disclose administering the vector prior, after, or at the same time of the DNA damaging agent. Thus, it would have been obvious to

one of ordinary skill in view of the teachings of Roth et al to administer the cell cycle blocking/synchronizing agent prior, after, or at the same time with the vector containing the therapeutic gene of interest to optimize the effect of the combination therapy.

Accordingly, the administration of the vector and cell cycle blocker/synchronizer of Son et al by alternative sequential administration of the combination therapy as suggested by Roth et al in order to obtain efficient delivery and optimal expression was within the ordinary skill in the art at the time of the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 38 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Son et al and Roth et al as applied to claim 15, 36-38 and 53-54 above, and further in view of Walker et al (U.S. Patent #6,041,252). Claims 15, 36-38 and 53-54 were rejected for the reasons as stated above. Son et al and Roth et al fail to teach a cell cycle blocking agent is in a liposome formulation. Walker et al disclose a method for delivering a therapeutic agent to a predetermined location in a host wherein a liposome-encapsulated therapeutic agent is administered to the host (abstract). Walker et al further disclose the use of liposomes to deliver drugs or other chemicals to specific target cells or groups of cells such that the drug or chemical is released into the target cells while minimizing entry of said chemicals or drugs into normal healthy cells (column 3).

Thus, one of ordinary skill would have been motivated to delivery therapeutic agent in a liposome formulation as suggested by Walker et al for specific targeting of cells or groups of cells with the treatment suggested by Son et al and Roth et al without affecting normal healthy cells for cancer treatment.

Accordingly, the method of cancer treatment of Son et al and Roth et al by delivering a therapeutic agent with liposome as suggested by Walker et al in order to optimize delivery to specific cells was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number~ is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Karen M. Hauda
Karen M. Hauda
Patent Examiner